MEDICAL PRACTICE

*Occasional Review***Handling of injectable antineoplastic agents**

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Summary and conclusions

Although the clinical toxicity of antineoplastic drugs has been well documented there is little or no information on the problems that may arise on the handling and mis-handling of such agents. This paper attempts to highlight the importance of taking precautions to prevent adverse effects resulting from contact with cytotoxic drugs during handling and to suggest a practical guide for the handling of such agents.

Introduction

In recent years there has been a huge increase in the use of antineoplastic agents, alone or in combination with other methods of treating neoplastic diseases. These agents may be divided into three main groups—steroids, immunostimulants, and cytotoxics. We propose to concentrate on the cytotoxic drugs, which may be classified as alkylating agents, anti-metabolites, or miscellaneous agents—for example, certain antibiotics, L-asparaginase, or heavy metal complexes.

Adverse effects of cytotoxic drugs

All of the cancer chemotherapeutic agents kill or impair susceptible tumour cells by blocking a drug-sensitive biochemical or metabolic pathway. Even in therapeutic doses, cytotoxic drugs produce toxic side effects due to poor selectivity between target cells and normal cells. Rapidly dividing cells are par-

ticularly damaged—for instance, those of the bone marrow, gut mucosa, hair follicles, germinal epithelium of the testes, thymus, and fetus. These toxic effects of the antineoplastic drugs are mediated directly by their antimitotic, or cytotoxic, properties and indirectly by their myelosuppressive or immunosuppressive action or both.¹ Some of these agents—for instance, fluorouracil—may also have photosensitising properties, but this is fairly uncommon. Another adverse effect of some of these drugs is the severe local irritation and ulceration caused by extravasation into the tissues outside a vein (see table). The thrombophlebitic potential of many of the intravenous cytotoxic drugs has been discussed elsewhere.³

Problems of handling

The aforementioned clinical toxicity of the antineoplastic agents has been well documented over the past decade.^{1 3-8} Many of these drugs, however, have a direct irritant effect on the skin, eyes, mucous membranes, and other tissues. Handled without due care, most cytotoxic drugs can cause local toxic or allergic reactions, or both, and the risks regarding carcinogenicity and mutagenicity should always be kept in mind by staff administering these drugs. There is little or no information published on the problems that may arise on the handling and mishandling of such agents. Two examples of such problems, however, are briefly discussed below.

When mustine hydrochloride is applied locally in conditions such as psoriasis or the treatment of mycosis fungoides, the precaution recommended in all articles is the wearing of rubber gloves by the doctor, nurse, or patient applying the mustine. Research carried out in Denmark⁹ showed that only one glove out of seven varieties tested gave any protection against the penetration of the mustine hydrochloride. This was the glove made of polyvinylchloride. Rubber gloves did not give protection, and a polyethylene glove also permitted penetration of mustine.

Cyclophosphamide is a pro-drug that requires metabolism in

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Precautions on handling antineoplastic drugs

Drug	Route of administration of injection	Comment	Effect on skin	Manufacturer's precautions on handling	Action on contamination
Actinomycin D (Cosmegen)	IV	Not carcinogenic but shown to be teratogenic	Extremely corrosive to soft tissues	Should only be given via tubing of a running intravenous infusion, which should be flushed immediately after administration. All precautions should be taken to avoid spillage on to skin—ie, gloves and goggles should be worn	Rinse off immediately in running water for 10 min and finally rinse with buffered phosphate solution ²
Azathioprine (Imuran)	IV	Potentially teratogenic and suspected to be carcinogenic	Solution is alkaline and very irritant to skin	Protective gloves and eye shields should be worn	Wash off with water as quickly as possible
Bleomycin	IM, IV, IA	Cytostatic	Poorly absorbed. Local toxic or allergic reactions	Wear protective gloves and mask and hold ampoule away from face	Rinse thoroughly with water
Colaspase (Crasnitin)	IV	Cytostatic. Not carcinogenic or teratogenic	Contact with skin should not cause any irritation	No special precautions for handling required	Wash affected area (skin, eyes, etc) very thoroughly with water
Cisplatin (Neoplatin)	IV	Carcinogenicity and teratogenicity suspected but not established	Skin reaction to platinum in sensitive patients	Gloves and mask necessary only if spillage occurs	Wash affected area thoroughly with water
Cyclophosphamide (Endoxana)	IV	Pro-drug that requires metabolism in liver before it becomes cytotoxic. Carcinogenic and teratogenic	Skin irritation is rare	No special precautions for handling	Wash affected area (skin, eyes, etc) very thoroughly with water
Cytarabine (Cytosar)	IV, SC, IT	Teratogenic. Causes corneal speckling if applied to eyes for several days	Not absorbed through intact skin	No special precautions for handling	Wash off affected area (skin, eyes, etc) with water
Dacarbazine (DTIC)	IV	Carcinogenic and teratogenic. Caution: Avoid extravasation on administration	Irritant. Avoid contact with skin and mucous membranes	Wear surgical gloves when reconstituting the drug into solution	Wash off skin with soap and water immediately. Irrigate eye with water
Daunorubicin (Cerubidin)	IV	Carcinogenicity and teratogenicity not established. Caution: Avoid extravasation on administration	Irritant. Avoid contact with skin and mucous membranes	Wear protective gloves when handling	Contamination should be treated by immediate thorough washing with water or isotonic saline
Doxorubicin (Adriamycin)	IV	Potential teratogen and carcinogenicity is suspected but not established. Caution: Avoid extravasation on administration	Irritant to skin but not absorbed into bloodstream	Protective gloves should be worn	Treat affected part immediately with copious lavage with water or soap and water
Ethoglucid (Epodyl)	IV, IA	Teratogenicity and carcinogenicity both suspected	Irritant (in undiluted form)	Wear protective gloves when diluting	Wash immediately with large amounts of water
Fluorouracil	IV infusion, IA	Oral administration commonly used with no untoward effects	Minor inflammatory reaction if skin is broken	No special precautions for handling	Flush affected parts with copious amounts of water
Ifosfamide (Mitoxana)	IV	Cytotoxic only after metabolism in liver. Teratogenic and carcinogenic	Irritation to skin and mucous membranes rare	No special precautions for handling	Affected area should be washed thoroughly with water
Melphalan (Alkeran)	IA, IV	Carcinogenic	Contact with skin should not cause any irritation	Wear protective gloves and eye protection	Solution of sodium carbonate 3% w/v should be used if spillage occurs
Methotrexate	IM, IV, IT, IA	Teratogenic and carcinogenic	Methotrexate has no vesicant effect on skin but is irritant, and contact with skin should be avoided	Surgical gloves should be worn	If skin is contaminated, wash off with water. Apply a bland cream (eg, Aqueous Cream BP) for any transient stinging. For systemic absorption of significant quantities, give calcium folinate (Leucovorin) cover
Mithramycin (Mithracin)	IV		Skin irritation is rare	No special precautions for handling are recommended	Affected area should be washed with water
Mitomycin (Mitomycin C)	IP, IA, IV	Teratogenic and suspected to be carcinogenic. Caution: Avoid extravasation on administration	Irritant effect on skin	Protective gloves to be worn	Thorough and immediate washing with large quantities of water. If eye is contaminated irrigate immediately with large amounts of water
Mustine	IV, IP, IA	Highly toxic	Mustine hydrochloride is a strong vesicant and a strong nasal irritant	Avoid contact with eyes and wear protective gloves	Wash skin with copious amounts of water or sodium carbonate 3% w/v or isotonic solution of sodium thiosulphate. If eyes contaminated wash out with large amounts of water and, if available, irrigate with sodium thiosulphate in isotonic solution (2.98% w/v)
Vinblastine (Velbe)	IV	Suspected to be teratogenic. Caution: Avoid extravasation on administration	Irritant effect on skin	Protective gloves should be worn when handling this drug	Thorough and immediate washing with large quantities of water. If accidental injection into sc tissues occurs, apply heparin (Hirudoid) cream to affected area
Vincristine (Oncovin)	IV	Suspected to be teratogenic. Caution: Avoid extravasation on administration	Irritant effect on skin	Protective gloves should be worn	As above
Vindesine (Eldisine)	IV	Suspected to be teratogenic. Caution: Avoid extravasation on administration	Irritant effect on skin. Corneal ulceration may result from accidental contamination	Avoid contact with eyes and wear protective gloves	As above

IV = Intravenous. IM = Intramuscular. IA = Intra-arterial. SC = Subcutaneous. IT = Intrathecal. IP = Intraperitoneal.

the liver before it becomes cytotoxic. Consequently, irritation to the skin or mucous membranes is rare, although there has been at least one recent report of a nurse developing an irritant reaction after accidentally spilling cyclophosphamide solution on her hands. A sensitive screening procedure that looked for mutagenic activity in the urine of nurses administering cytotoxic drugs¹⁰ showed that most of the nurses exhibited mutagenicity in their urine concentrates. These two reports highlight the importance of taking precautions to protect personnel preparing and administering cytotoxic drugs.

In the light of this evidence it was thought that some advice for nursing and medical staff on the precautions to be taken while handling injectable carci-nochemotherapeutic agents would be both useful and necessary to prevent accidents arising on the wards. The manufacturers of these agents were requested to provide information on the irritant nature of their product and on the action to be taken if contact with the skin, eyes, or mucous membranes occurred. The general advice given was that the nurse should avoid contact with the injection solution by wearing protective gloves, and eye protection was also advised. Ampoules should be held away from the face during opening and preparation of the solution for injection. Similar precautions apply to a pharmacist making extemporaneous cytotoxic or cytostatic preparations. When making capsules and suspensions, etc, a mask to prevent inhalation of powder and gloves to avoid skin contact should be worn.

The following list of precautions on handling injectable antineoplastic drugs, details of the effect of spilling some of the solution on the skin, and the action to be taken on contamination has been compiled from personal communication with the manufacturers of each drug.

Management of spillage of cytotoxic drugs

Every oncology unit and pharmacy should be prepared to deal with the spillage of cytotoxic solutions and powders. The following procedure has been suggested by one manufacturer¹¹ for managing spillage of their particular anticancer agents, and this general procedure would seem to be appropriate for all cytotoxic drugs.

- (1) Put on rubber or polythene gloves.
- (2) If there is visible powder spill wear a face mask.
- (3) Place spilled materials in a polythene bag.
- (4) Wipe up remains with damp cloth or cotton waste and place in bag.
- (5) Seal bag. Place in second bag and seal.
- (6) Label bag, stating contents and mark *danger*.
- (7) Wash contaminated surfaces with copious amounts of water and exposed skin areas with soap and water.
- (8) Dispose of washing materials used as in 3-6 above.
- (9) Send waste for disposal by incineration.
- (10) NB. Only massive spillage is likely to lead to a health hazard.

DISPOSAL

A problem that arises on the ward concerns the disposal of small quantities of cytotoxic drugs in instances where a patient does not receive the total contents of an ampoule. Some cytotoxic drugs are dangerous if incinerated while others should be neutralised in some way before disposal in the public water supply.

In 1977 the manufacturers of cytotoxic injections were asked for their recommendations for the disposal of their products. The usual recommendation is to flush the drug through the drainage system with copious amounts of water. In view of the small quantities, the considerable dilution factor, and the continual presence of naturally excreted drug metabolites in sewage, it is doubtful whether proper disposal of any drug in this way would constitute a health hazard.

It appears that oncology units in hospitals exercise different degrees of caution with respect to the handling of cytotoxic drugs, although some units do require staff to take certain protective measures. There is little scientific evidence on which to base any recommendation, but until we know a little more of the hazards, it would be wise to be cautious when handling these drugs.

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A man aged 65 with maturity-onset diabetes had a coronary attack three and a half years ago without infarction and no further disability from that. The diabetes, however, gradually became worse, with oral treatment—glibenclamide (Daonil)—gradually becoming ineffective. He has now developed a large liver and raised serum transaminase concentrations. What might be the cause of this and what treatment is advised?

The abnormal transaminases suggest some form of parenchymal liver disease, either hepatitis or cirrhosis. Aetiological factors that should be considered are alcohol, drugs, hepatitis B, and iron overload. Accumulation of fat in the liver due to poor control of the diabetes is less likely. Investigations might include γ -glutamyl transferase, serum iron and total iron binding capacity, tests for hepatitis antigens, and liver biopsy. It is not possible to advise about treatment until the cause of the hepatomegaly is established.

How can you differentiate episcleritis from scleritis, and what systemic disorders are these conditions associated with?

Episcleritis is a mild superficial inflammation of the connective tissue just deep to the conjunctiva. It may be either flat or nodular and produces an area of redness on the surface of the eye that is sore but not really painful. The inflammation is not severe. Scleritis is a very serious disorder that affects the deep scleral tissue itself, either anteriorly or posteriorly. The sclera becomes oedematous, and the overlying episclera is often also inflamed. The sclera may become necrotic and, either after acute inflammation or as a primary condition, this may lead to a loss of scleral tissue (scleromalacia perforans). Scleritis is extremely painful, the pain radiating from the eye and often keeping the patient awake at night. The eye appears very red and inflamed if the inflammation is anterior and the sclera and overlying tissues are oedematous. The tendency to necrosis can lead to a perforation of the eye and sometimes to loss of the eye despite energetic surgical "patching" treatment. Both these types of inflammation are sterile, and they are most commonly found as accompaniments of collagen diseases, although mild episcleritis is also found as an isolated defect.

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